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Developmental Profile in a Patient With Monosomy 10q and Dup(17p) Associated With a Peripheral Neuropathy

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We report on a patient with dup(17p) and monosomy (10q) resulting from a familial translocation. Manifestations typical of both syndromes were present. The overall development of this patient was better by comparison with similar reported cases of either anomaly. Our evaluation detected severe gross motor delay and signs of a demyelinating peripheral neuropathy. This patient is trisomic for the region of 17p which includes the peripheral myelin protein-22 (PMP-22) gene, known to be duplicated in Charcot-Marie-Tooth neuropathy type 1A (CMT1A). Our analysis in this patient suggests that trisomy for the PMP-22 gene led to the demyelinating neuropathy and contributed to his severe motor developmental delay.

KEY WORDS: dup(17p), monosomy 10q, developmental disability, Charcot-Marie-Tooth neuropathy type 1A, PMP-22 gene, gene dosage

INTRODUCTION

We report on a child with monosomy 10q and dup(17p) resulting from an apparently balanced maternal translocation t(10;17)(q26.3;p11.2). Manifestations of the dup(17p) and monosomy 10qter syndromes were present; however, the overall development was better than that previously reported in either syndrome. The patient's motor development was significantly more impaired than cognitive development and signs of a peripheral neuropathy were found. This led to an analysis of the Charcot-Marie-Tooth type 1A (CMT1A) gene region on chromosome 17p11.2-12. The CMT1A gene region is associated with a tandem 1.5 Mb duplication which includes the peripheral myelin protein-22 (PMP-22) gene [Lupski et al., 1991].

CLINICAL REPORT

The patient is the third child born to a 39-year-old G6P3(SAB 3) mother and 35-year-old father. The family history is unremarkable and there is no consanguinity. An elevated serum alpha-fetoprotein (AFP) level was detected at 16 weeks. The amniocentesis karyotype was interpreted as 46,XY,10q+. The father's chromosomes were normal. The mother had a balanced translocation 46,XX,t(10;17)(q26.3;p11.2). Prenatal ultrasound at 7 months demonstrated possible hydrops which resolved by term.

The infant was born normally at 37 weeks of gestation. Apgar scores were 9 at one minute and 10 at 5 minutes. Birth weight was 2,784 g (25th centile) and length 46 cm (25th centile). Bilateral inguinal hernias and hydroceles were present. An echocardiogram demonstrated a ventriculoseptal defect (VSD) and bicuspid aortic valve.

Past medical history was significant for failure to thrive, esophagitis, gastroesophageal reflux, hiatal hernia, frequent otitis media, upper respiratory infections, and reactive airway disease. Surgical procedures included a Nissen fundoplication with gastrostomy tube, bilateral herniorraphy and hydrocele repair, tonsillectomy, and adenoidectomy with bilateral myringotomy tube placement; the VSD closed spontaneously. Evaluation of motor function prompted a magnetic resonance image (MRI) scan of the spine which was normal. A head MRI demonstrated a hypoplastic corpus callosum, and slightly increased amount of fluid near the cerebellum.

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At age 27 months the infant was admitted to an inpatient feeding program and was referred for further evaluation. Length was 85 cm (5th centile), weight 9.8 kg (<5th centile, 50th centile for 11 months), and OFC was 45.5 cm (<5th centile, 50th centile for 9 months). The head was long with a triangular face (Fig. 1). Downslanting palpebral fissures, a short philtrum, high arched palate, wide-spaced teeth, and a small nose with anteverted nares were noted. The nipples were wide spaced and underdeveloped. The phallus was small (3 cm, 10th centile), with an underdeveloped scrotum and descended testes. The anus was anteriorly placed. He had 2, 3 cutaneous syndactyly on both feet, and a short right 5th metatarsal. The thumbs were proximally placed with tapering of the 4th and 5th fingers. The palms were long (7 cm, >97th centile) with short fingers (hand length 10.5 cm, 50th centile). Fifth finger clinodactyly was noted bilaterally. There were 7 whorls and 3 ulnar loops on the fingertips. The axial triradii were medially placed on the right, and distally on the left.

Neurologic exam revealed hypotonia and absent deep tendon reflexes. Strength was mildly decreased in the upper, compared to the lower limbs. There was no muscular atrophy. Cranial nerves were normal.

DEVELOPMENTAL STATUS

Delayed motor development associated with significant hypotonia was noted during the first 6 months of life. At age 28 months, the patient was able to sit unsupported for prolonged periods, and could stand briefly with assistance, but could not take steps. Standardized testing (Table I) revealed age equivalents of 8 and 12 months for gross motor and fine motor skills, respectively.

Fig. 1. Photo of patient at age 27 months. Note triangular face, down-slanting palpebral fissures, and small anteverted nose.

TABLE I. Summary of Developmental Testing Results*

Test	Result
Revised Gesell Developmental Schedules	
Gross motor	CAE: 9 months
Fine motor	CAE: 12 months
Adaptive	CAE: 14 months
Clinical Linguistic and Auditory Milestone Scale/Clinical Adaptive Test	
CLAMS	CAE: 16 months
CAT	CAE: 14.7 months
Preschool Language Scale-3	
Receptive Language	CAE: 15 months; SS: 74
Expressive Language	CAE: 13 months; SS: 69
Bayley Scales of Infant Development	
Mental Scale	CAE: 14
Vineland Adaptive Behavior Scales	
Communication	SS: 56
Daily Living Skills	SS: 52
Socialization	SS: 57
Motor Skills	SS: 52
Composite	SS: 50

*CAE, chronologic age equivalent; SS, standard score.

Communication/socialization skills were much less delayed. At age 28 months, he could respond to one-step commands without gestural cues and could indicate body parts by pointing. He used single-syllable phrases to consistently indicate some words, and used signs for others. He was able to initiate gesture games and engaged in parallel play. Standardized testing (Table I) yielded age-equivalent scores for receptive language, play, and socialization skills in the 14–16-month range, with scattering of abilities to 18 months. Adaptive skills, except for those involving more refined fine motor coordination, were at a 14-month level.

At age 28 months, the patient's overall development was consistent with that of a child at 14 months, yielding a developmental quotient of 0.50. (Development quotient = developmental age/chronological age.)

ELECTROPHYSIOLOGIC STUDIES

Electrodiagnostic studies were performed at age 28 months using routine surface recording electrodes. Sensory nerve action potentials were unelicitable. The compound muscle action potentials were markedly diminished: 1.1 mV, median, 0.7 mV peroneal. Motor nerve conduction velocities were also severely reduced: 6 m/sec median and 5.0 m/sec peroneal. Normal values for children of this age from our laboratory are >40 m/sec and >38 m/sec for median and peroneal motor conduction velocities, respectively. Slowing was homogenous among comparable nerve segments and along the course of individual nerves. These electrophysiologic findings were felt to be indicative of a severe, genetically determined demyelinating sensory-motor neuropathy.

MATERIALS AND METHODS

Under a protocol of informed consent (The Children's Hospital of Philadelphia), blood was obtained from the

patient and parents for preparation of karyotypes, DNA isolation, and constitution of Epstein-Barr virus-transformed cell lines by standard techniques. A molecular analysis of patient and parental DNA was carried out with markers which are known to map to the CMT1A gene region on chromosome 17p11.2-12. Markers VAW409R3(D17S122), VAW412(D17S125), and EW401(D17S61) are duplicated in patients with CMT1A, while marker EW301(D17S58) maps proximal to the duplication [Lupski et al., 1991; Raeymaekers et al., 1991, 1992]. The PMP-22 gene (probe p132G8R1) maps within the duplicated region and is proposed to cause CMT1A by either dosage effect or mutations within the gene. Gene copy number was estimated by visual inspection of polymorphic bands on autoradiograms. The karyotype was obtained from peripheral blood lymphocytes and G-banded by standard techniques.

RESULTS

Cytogenetic Analysis

A partial karyotype of the patient is shown in Figure 2. The patient's father has a normal karyotype. The mother is the carrier of an apparently balanced reciprocal translocation between chromosomes 10 and 17. The patient inherited a normal chromosome 17 from both parents, and the derivative chromosome 10 from his mother, resulting in partial trisomy 17p and monosomy 10q. His karyotype is 46,XY,−10,+der(10)t(10;17)(q26.3;p11.2)mat.

Molecular Analysis

Probe p132-G8R1 (a genomic subclone of the PMP-22 gene) detects polymorphic alleles at 11 and 9.6 kb with *Eco*RI/*Hinc*II digestion [Patel et al., 1992]. The patient has increased hybridization intensity of the 11 kb band relative to the 9.6 kb band, indicating trisomic dosage for the PMP-22 gene (Fig. 3). Probes EW409R3 (D17S122) and EW401(D17S61) detect polymorphic alleles with *Msp*I, and map within the CMT1A duplication region flanking the PMP-22 gene [Chance et al., 1992; Matsunami et al., 1992]. The patient and his parents are heterozygous at these loci. Probe EW409R3 (D17S122) detects polymorphic alleles of 2.8, 2.7, and 1.9 kb [Wright et al., 1990; Raeymaekers et al., 1992]. The patient has increased intensity of the 2.8 kb band relative to the 1.9 kb band, suggesting trisomic dosage at the VAW409R3 locus. The father has a 2.7 and 1.9 kb band. The mother was homozygous with 2 copies of a 2.8 kb band. EW401 (D17S61) detects polymorphic alleles with *Msp*I at 5.5-kb and 4.4-kb, and in the patient there was increased intensity of the 5.5 kb band relative to the 4.4 kb band, indicating trisomic dosage for this marker. Probe EW301 (D17S58) detects polymorphic alleles of 10 and 8 kb with *Bgl*II but was homozygous in our patient and his parents. The results indicate that the patient is trisomic for a major portion of the region of 17p that is duplicated in CMT1A patients, including the PMP-22 gene.

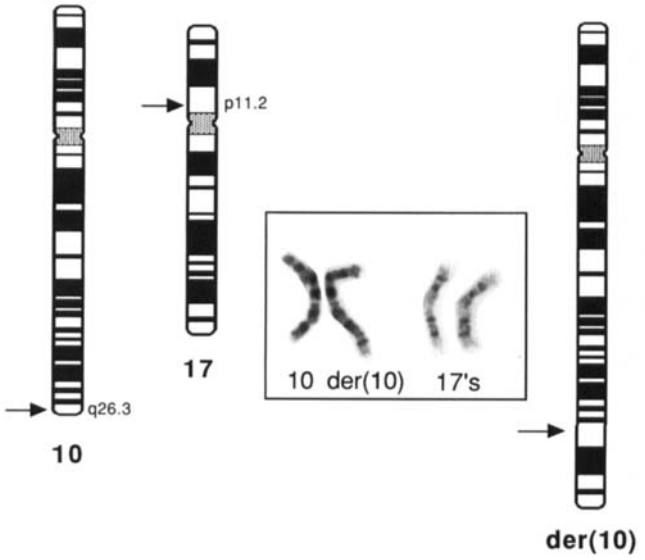

Fig. 2. Partial karyotype of translocation. Idiogram demonstrates formation of the der(10).

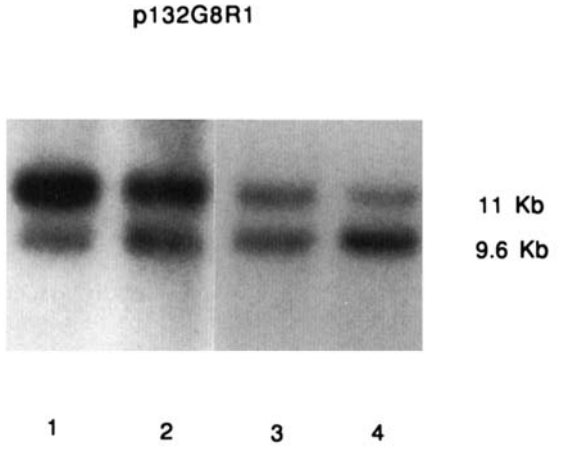

Fig. 3. Autoradiograph of parental and patient DNA digested with *Eco*RI/*Hinc*II and hybridized with p132G8R1. Lengths of DNA fragments are indicated in kilobases. **Lane 1:** Patient; **lane 2:** father; **lane 3:** mother; **lane 4:** CMT1A control. Note the increased intensity of the 11 kb fragment relative to the 9-6 kb fragment in the patient, suggesting trisomy at this locus.

DISCUSSION

We describe a patient with multiple congenital anomalies including a bicuspid aortic valve, VSD, hiatal hernia, failure to thrive, areflexia, and minor anomalies. The patient's developmental progress has been surprisingly good, compared to that documented on patients in previously reported cases of dup(17p) or monosomy (10q). At 28 months of age, overall development was consistent with an age-equivalent level of 14 months. However, his motor skills were more significantly impaired than cognitive skills leading us to further evaluation. Clinical findings of areflexia and prolonged nerve conduction velocities were consistent with a demyelinating motor and sensory neuropathy.

CMT1A is associated with a tandem 1.5 Mb duplication in chromosome 17p11.2-p12 in most CMT1A patients [Lupski et al., 1991; Raeymakers et al., 1991].

The CMT1A duplicated region includes the PMP-22 gene. Demyelinating neuropathy has been reported in 3 patients with total or partial trisomy of chromosome 17p [Chance et al., 1992; Lupski et al., 1992; Upadhyaya et al., 1993]. Our patient also had 3 copies of the PMP-22 gene (Fig. 3), adding further evidence to support gene dosage as a mechanism for CMT1A. Two of the previously reported cases had a de novo duplication of 17p11.2-p12 and either had profound developmental delay [Lupski et al., 1992] or a global pattern of delay with a developmental quotient of 56 [Upadhyaya et al., 1993]. The third patient with dup(17p) had marked mental retardation at 14 years of age, and was previously reported at 41 months to test at a 12-month level on a Denver Developmental Standardized Test [Feldman et al., 1982; Chance et al., 1992]. The duplication in our patient extends more proximally than the PMP-22 gene, since he is trisomic for nearly the entire p arm of chromosome 17. We hypothesize that the demyelinating neuropathy seen in our patient results from trisomy of the PMP-22 gene, and in the setting of dup(17p)/monosomy (10q) likely contributes to the severe motor delays.

Dup(17p) is a rare condition reported only 7 times [Latta and Hoo, 1974; Bartsch-Sandhoff and Hieronimi, 1979; Feldman et al., 1982; Jinno et al., 1982; Martsolf et al., 1988; Schrander-Stumpel et al., 1990; Spinner et al., 1993]. Our patient has some of the previously reported clinical findings of this disorder including failure to thrive, microcephaly, wide-spaced nipples, clinodactyly, high arched palate, small teeth, and congenital heart disease. Although detailed developmental information is not available, all reported patients with dup(17p) were mentally retarded as described below.

The first reported patient [Latta and Hoo, 1974] was severely retarded and died at 2 years of age from pneumonia (as noted on follow-up by Bartsch-Sandhoff and Hieronimi [1979]). A 16-month-old male had severe developmental retardation [Bartsch-Sandhoff and Hieronimi, 1979], a 6-month-old male was estimated at a 2-month level [Jinno et al., 1982], a 3-month-old female had evidence of psychomotor retardation but died at 4 months [Schrander-Stumpel et al., 1990], and another female had severe psychomotor retardation on subsequent exams [Martsolf et al., 1988]. The remaining patient died neonatally [Spinner et al., 1993].

Terminal deletions of 10q have been reported in 26 patients resulting in a definite phenotype [Wulfsberg et al., 1989]. Our patient shares some of these manifestations which include postnatal growth retardation, microcephaly, down-slanting palpebral fissures, clinodactyly, syndactyly, congenital heart disease, and urogenital anomalies.

The developmental data on 20 patients with monosomy 10q have been reviewed but a specific psychological profile could not be delineated [Schrander-Stumpel et al., 1991]. Subsequently 2 new patients were reported [Wilkie et al., 1993]. Of the 22 reported children who survived the neonatal period, most had severe mental retardation. All 7 of the reported infants had "obvious" or severe developmental delay [Mulcahy et al., 1982; Shapiro et al., 1985; Chieri and Iolster, 1983; Curtis et al., 1985; Greenberg et al., 1988; Fryns et al., 1989], 3 of 4 toddlers had moderate developmental delay [Evans-Jones et al., 1983; Zatterale et al., 1983; Wilkie et al., 1993], and the fourth had mild global delay at age 18 months [Gorinati et al., 1989]. In the older age group, 4 of 11 had severe mental retardation [Lewandowski et al., 1978; Turleau et al., 1979; Shapiro et al., 1985; Wulfsberg et al., 1989], one had moderate to severe mental retardation [Wilkie et al., 1993], 4 had moderate retardation [Schrander-Stumpel et al., 1991; Mehta et al., 1987; Curfs, 1989], and 2 had speech impairments without further developmental data given [Greenberg et al., 1988].

Our patient has the findings of both chromosomal syndromes, and a peripheral neuropathy likely associated with trisomic expression of the PMP-22 gene. The striking aspect of his developmental status is his relatively advanced socialization and receptive language skills in contrast to his motor delay. Thus, the cognitive development in dup(17p) may be variable and not as severe as previously described. This has important implications for counseling families. In addition, attention to such variation from the expected, in children whose developmental disability is on the basis of a cytogenetic imbalance, may lead to further elucidation of other contributory genes.

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